congestive heart failure. This leads to increased production of the vasoconstrictor angiotensin II and increased release of aldosterone and norepinephrine. In some patients, arginine-vasopressin levels are also higher than normal. Vasoconstriction mediated by these neuroendocrine systems are, to some extent, counterbalanced by increased production of vasodilator prostaglandins and the vasodilator, atrial natriuretic peptide. In most symptomatic patients, however, the vasoconstrictor influences predominate, causing a net increase in systemic vascular tone.

Vasodilators have a variety of mechanisms of action. These include the following: antiadrenergic drugs (α-receptor blocking agents, in particular), β_2-receptor agonists, vasopressin antagonists, serotonin antagonists, prostaglandins, calcium entry blocking agents, angiotensin-converting enzyme inhibitors and the direct-acting vasodilators. Hemodynamic studies using these agents usually show initially improved systemic hemodynamics and cardiac performance. Long-term clinical benefit, however, does not occur with all vasodilators. Direct-acting arteriolar vasodilators such as hydralazine or minoxidil, when used alone, do not improve the exercise capacity or clinical state significantly in patients with chronic congestive heart failure. α-Receptor blocking agents such as prazosin hydrochloride are also ineffective in most patients. In contrast, isosorbide dinitrate and the angiotensin-converting enzyme inhibitors, captopril or enalapril maleate, improve the clinical state and exercise tolerance in most patients. Recently a Veterans Administration cooperative trial has reported that a combination of hydralazine, 300 mg a day, and isosorbide dinitrate, 160 mg a day, can improve survival of patients with mild to moderately severe chronic congestive heart failure.

Based on these reports, either a combination of hydralazine with nitrates or angiotensin-converting enzyme inhibitors should be considered in the "unloading" therapy for chronic heart failure. A lack of comparative studies prevents making a clear choice between these approaches, although correcting neuroendocrine abnormalities more effectively by using angiotensin-converting enzyme inhibitors may favor the latter.

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Treatment of Gram-Negative Bacterial Meningitis

THE THIRD-GENERATION cephalosporin antibiotics have greatly improved the prognosis for adult patients with gram-negative bacillary meningitis. Before 1980, when aminoglycoside antibiotics and chloramphenicol were used extensively, case-fatality rates ranged from 40% to 90%. Since the third-generation cephalosporins were introduced, case-fatality rates have fallen dramatically; in fact, cure rates of 75% to 90% have become the rule. Of these agents, cefotaxime sodium and moxalactam disodium have received the most usage for this indication. Available data suggest that ceftriaxone sodium, ceftazidime and ceftizoxime sodium offer comparable efficacy. These antibiotics show potent bactericidal activity against not only *Escherichia coli* and *Klebsiella pneumoniae*, the leading pathogens, but also against many other Enterobacteriaceae. Minimum inhibitory concentrations range from 0.01 to 1.0 μg per ml for most genera of this family except *Enterobacter*. In patients with meningitis, drug concentrations in cerebrospinal fluid (CSF) greatly exceed these minimum inhibitory concentrations: peak concentrations generally range from 10 to 40 μg per ml. Thus, unlike aminoglycoside antibiotics or chloramphenicol, third-generation cephalosporins produce CSF antibiotic concentrations that are 20 to 100 times the minimum inhibitory concentration of the infecting bacterium, and they rapidly sterilize the CSF.

Despite the successes of third-generation cephalosporins, meningitis caused by certain species of gram-negative bacilli remains a difficult and somewhat controversial therapeutic problem. The most troublesome organisms include the more resistant Enterobacteriaceae, such as *Enterobacter cloacae*, as well as certain non-Enterobacteriaceae, notably *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus*. Therapy for infections caused by these organisms is optimally based on the results of quantitative susceptibility tests. As a general rule, when minimum inhibitory concentrations of the third-generation cephalosporins for the pathogen are greater than 1.0 μg per ml, patients require the most active third-generation cephalosporin or extended-spectrum penicillin plus the most active aminoglycoside antibiotic. Trimethoprim-sulfamethoxazole may be useful against some organisms, such as *A calcoaceticus*. Aminoglycoside antibiotic administration by both intravenous and intralumbar routes is recommended. Intraventricular administration through a reservoir should be considered for patients who have relapsed or responded poorly to other regimens.

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Home Intravenous Antibiotic Therapy

HOME INTRAVENOUS (IV) ANTIBIOTIC THERAPY presents an opportunity to provide hospital level therapy at a substantially lower cost while enabling patients to resume a near-normal life-style.

Proper patient selection is the cornerstone of successful home therapy. Patients appropriate for home treatment have no indications for hospital care other than the need to receive antibiotics intravenously. Common infections treated are osteomyelitis, septic arthritis, diabetic foot infections, endocarditis (after inpatient observation) or any other conditions wherein patients are medically stable except for an infection requiring IV administration of antibiotics.

Efficacy is the primary consideration for antibiotic selection in any treatment setting, but one must additionally adjust dosing times to accommodate patients' sleep patterns and use

regimens that minimize infusion frequency. Cefazolin, cefonicid sodium, cefoperazone sodium and ceftriaxone sodium are used extensively because their infrequent dosing requirements, safety and spectrum match many conditions amenable to home therapy.

A competent, effective IV therapy team is another critical component of this technique. IV therapists need to have both expert nursing skills and knowledge regarding potential toxicity. They must remain readily available to patients on a 24-hour basis and possess strong teaching skills so that patients develop confidence and judgment.

Issues still to be standardized are the optimal organization of home care agencies, patient and diagnosis qualification criteria, standards of care for physicians and agencies, reimbursement and liability exposure.

In the final analysis, home IV therapy makes sense in today's thrust toward providing as much care as is safe and feasible outside hospital. It synergizes with the public impulse to accept more responsibility for personal fitness and health. To invoke this new modality, physicians need only blend their current expertise and sound medical judgment with the special considerations for home therapy summarized above. When home IV antibiotic therapy is done well, everyone benefits.

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Vaccination for Hepatitis B

TWO SAFE VACCINES containing purified hepatitis B surface antigen (HBsAg) are now available for preventing hepatitis B infection. The first vaccine is derived from the plasma of screened, healthy HBsAg carriers. Even though extensive tests show that all known viruses are inactivated by the vaccine preparation process, many patients and health care providers have been reluctant to use this plasma-derived vaccine because of concerns about the acquired immunodeficiency syndrome. The second vaccine, released in early 1987, is prepared from recombinant DNA propagated in yeast. The recombinant vaccine, because it is not plasma derived, has had greater acceptance but has no other advantages and has a similar level of safety and cost. Concerns about long-term efficacy of the yeast-recombinant vaccine have been raised because of reduced antigenicity when compared with plasma-derived HBsAg.

Protective levels of antibody to HBsAg develop in about 85% to 95% of vaccinated healthy adults, who receive three doses of vaccine intramuscularly in the deltoid. Antibody levels tend to be lower if the injections are given in the buttock or to patients who are immunologically compromised. For those who have the usual anti-HBsAg response, protection approaches 100%. The duration of protective antibody levels is not yet known and booster doses may be required at some future time.

There are no known adverse or beneficial effects to vaccinating previously infected persons. Thus, the decision to screen potential vaccinees (using either hepatitis B core antigen or anti-HBsAg) is an economic one, based on the cost of screening tests and vaccination versus the likelihood that a patient has previously had hepatitis B.

Hepatitis B vaccine is recommended for persons at increased risk of hepatitis B developing. Potential vaccinees include homosexually active men, users of illicit injectable drugs, hemodialysis patients, selected immigrants, prisoners, institutionalized retarded persons, recipients of factor VIII or IX concentrates, long-term transfusion recipients, household and sexual contacts of hepatitis B carriers and health care workers with frequent exposure to blood or blood products.

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Intraperitoneal Chemotherapy for Ovarian Cancer

OVARIAN CANCER is the most common fatal gynecologic malignant disorder in the United States and the fourth leading cause of cancer death in women, with 18,000 new cases and 11,000 deaths per year. About 80% of patients with ovarian cancer have advanced disease (stage III or IV) at diagnosis. With the introduction of cisplatin-based combination chemotherapy administered systemically, surgically documented complete response rates of 20% to 30% can now be achieved. Few of these responses, however, result in long-term relapse-free survival (seven-year survival rate less than 15%).

Ovarian cancer is a disease that tends to remain confined to the peritoneal cavity even in its most advanced stages. This makes it particularly amenable to regional methods of drug delivery. A recently developed technique for treating advanced ovarian cancer has been the direct intraperitoneal administration of chemotherapeutic agents. One of the major principles of intraperitoneal chemotherapy is to administer the anticancer agent in a large fluid volume of a normal saline solution (two liters) to ensure adequate drug distribution throughout the peritoneal cavity. Another is to administer agents known to be active against ovarian cancer when administered systemically. With intraperitoneal administration, high drug concentrations can be achieved in the area of the tumor while corresponding systemic levels are much less, resulting in less drug exposure to normal tissues. This results in an enhancement of the drug's therapeutic index. We have used a totally implantable drug delivery system for intraperitoneal drug administration in our studies. It consists of a Tenckhoff catheter attached to a Port-a-Cath portal (Pharmacia Nu Tech).

The most active single agent for the treatment of ovarian cancer is cisplatin. We have conducted a series of intraperitoneal cisplatin-based chemotherapy trials over the past several years. Agents that we have used in combination with cisplatin have included cytarabine and, most recently, etoposide. These studies have been done in patients with persistent disease following administration of at least six cycles of intravenous cisplatin-based chemotherapy. Two important conclusions have emerged from these studies. First, the intra-